



Recessive multiple epiphyseal dysplasia – Clinical characteristics caused by rare compound heterozygous *SLC26A2* genotypes

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ABSTRACT

Pathogenic sequence variants in the solute carrier family 26 member 2 (*SLC26A2*) gene result in lethal (achondrogenesis Ib and atelosteogenesis II) and non-lethal (diastrophic dysplasia and recessive multiple epiphyseal dysplasia, rMED) chondrodysplasias. We report on two new patients with rMED and very rare compound heterozygous mutation combinations in non-consanguineous families. Patient I presented in childhood with waddling gait and joint stiffness. Radiographs showed epiphyseal changes, bilateral coxa plana-deformity and knee valgus deformity, for which he underwent surgeries. At present 33 years his height is 165 cm. Patient II presented with cleft palate, small jaw, short limbs, underdeveloped thumbs and on radiographs, cervical kyphosis with an underdeveloped C4. He also developed severe scoliosis but has grown at -2.9 SD curve. Molecular analysis revealed that patient I is heterozygous for two known pathogenic variants in *SLC26A2*, a splice site variant c.-26+2T > C and a missense variant c.1957T > A (p.Cys653Ser), while patient II is compound heterozygous for missense variants c.835C > T (p.Arg279Trp) and c.1535C > A (p.Thr512Lys). These patients further elucidate the variability of the phenotypic and genetic presentations of rMED.

1. Introduction

Autosomal recessive multiple epiphyseal dysplasia (rMED; OMIM #226900) is a rare and relatively mild form of chondrodysplasia caused by mutations in *SLC26A2* (OMIM 606718) (Superti-Furga et al., 1999) (Mäkitie et al., 2003). Solute carrier family 26 member 2 (*SLC26A2*) is a transmembrane sulfate carrier protein that partakes in sulfation of proteoglycans by transporting sulfate into the cartilage matrix. Mutations in *SLC26A2* result in inappropriately constructed cartilage matrix; undersulfated proteoglycans hamper bone development especially at long bones epiphyses, large joints, and metacarpals and metatarsals. To date, 51 different *SLC26A2* mutations have been reported to associate with four chondrodysplasias: achondrogenesis Ib, atelosteogenesis II, diastrophic dysplasia (DTD) and rMED. The most frequent *SLC26A2* mutation in the Finnish population, where DTD is exceptionally common, is c.-26+2T > C, also known as the Finnish founder

mutation (Hastbacka et al., 1999). In other populations, the most prevalent mutation is c.862C > T (p.Arg279Trp) (Syvanen et al., 2013).

The phenotype of rMED varies according to the type of *SLC26A2* mutation (Czarny-Ratajczak et al., 2010). The main clinical features include normal to mildly short stature, joint contractures, clubfeet, shortening of limbs and waddling gait; radiographs show epiphyseal dysplasia (Bonafe et al., 2008) (Mäkitie et al., 2003). Recent reports suggest a wider spectrum of clinical manifestations, including cleft palate and auricular deformities (Mäkitie et al., 2015).

Here we present two patients, a 33-year-old and a 5-year-old male, with rMED due to very rare compound heterozygosity for *SLC26A2* mutations. Both have relatively normal growth but show also manifestations that are more typical for DTD rather than rMED, further evidencing a clinical overlap of these conditions.

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2. Clinical report

This retrospective study is part of an ongoing research program on epidemiological, clinical and genetic characteristics of skeletal dysplasia in Finland, carried out at Children's Hospital, Helsinki University Hospital, Finland. The protocol was approved by the Institutional Research Ethics Committee. The two patients had been followed at various clinics at Helsinki University Hospital (Patient I) and Turku University Hospital (Patient II) and were referred to the Clinical Genetics Department, Helsinki University Hospital in 2017 for further evaluation.

The patients' data from hospital records were reviewed for clinical presentation, disease progression, anthropometry and radiographic skeletal manifestations. Growth data were compared with Finnish growth standards. Genetic studies were performed from peripheral blood genomic DNA; for patient I, a gene panel including *SLC26A2* was performed at Blueprint Genetics (Helsinki, Finland) and the identified *SLC26A2* variants were confirmed by Sanger sequencing. For patient II, *SLC26A2* was screened at HUSLAB (Helsinki, Finland) for two Finnish major mutations and subsequently for all exons.

2.1. Patient I

This presently 33-year-old man was born at full term to non-consanguineous parents who were healthy and normal in height. The birth measurements were normal: length 49 cm (-1.2 standard deviation units, SDS), weight 3845 g ($+0.3$ SDS), and head circumference 36.5 cm ($+0.8$ SDS). He was treated for bilateral hip dysplasia after birth. He walked at 12 months but due to abnormal gait, he underwent clinical investigations at 2 years. He was noticed to have diffuse skeletal epiphyseal changes that were most prominent in his lower limbs; he had bilateral coxa plana deformity and his knees were in valgus position. Despite normal spine, he was diagnosed with spondylo-epiphyseal dysplasia; no molecular diagnosis was performed. During childhood he underwent surgeries to correct his knee valgus deformity and hip and knee surgeries are presently considered because of joint pain. Other joints and the spine are less severely affected and only exhibit mild stiffness and restricted range of motion. His hands and feet are slightly wide and stubby and both fourth metacarpals and metatarsals are short. There is no clubfoot deformity. He has no apparent facial dysmorphias, extra-skeletal abnormalities or dental problems, and has normal vision, hearing and intelligence. He has no scoliosis and has reached an adult height of 165 cm (-2.5 SDS).

Radiographs between 6 and 33 years of age were reviewed (Fig. 1). At 6 years, he had flat crescent-shaped femoral epiphyses, abnormally broad and short femoral necks, and a dysplastic right acetabulum. Epiphyses and metaphyses of the knees were abnormal. The double layer patellae were laterally displaced. All metacarpals, especially the fourth, were short. Epiphyses of both radius and ulnae were slightly flat. Lumbar vertebrae were of normal height and shape. At 18 years he had developed bilateral severe hip arthrosis and the right femoral head was cranially dislocated. At 33 years the patient had marked arthrosis in both hips and knees.

2.2. Patient II

This presently 5-year-old boy was born by elective Caesarian section at 38 + 6 gestational weeks from breech position measuring 47 cm (-1.9 SDS) and 3230 g (-0.8 SDS); his head circumference was 35.5 cm ($+0.3$ SDS). The parents were non-consanguineous, healthy and normal in height. Routine ultrasounds during pregnancy showed normal morphology and growth. Immediately after birth, he was noticed to have a wide cleft palate exposing inferior nasal structures, small jaw suggesting Pierre Robin-sequence, overall short limbs and length, spontaneous palmar ulnar deviation and underdeveloped thumbs (Fig. 2). Ultrasound showed femoral heads to be abnormal in shape.

Cervical radiographs indicated kyphosis with an underdeveloped C4. Cleft palate was closed at 1 year and his jaw has grown spontaneously. He developed severe progressive scoliosis during the second year and was treated with casting and a corset until present age.

Presently, at 5 years, his height is 98 cm (-3.0 SDS) and weight 19 kg (0 SDS) (Fig. 2). He has developed significant valgus deformity at knees. His ankles are stiff but there is no clubfoot deformity. Joint stiffness is also present in upper limbs and he has contractures in both third fingers. Both earlobes are slightly thick and low set. His head circumference is normal (-0.5 SDS).

On radiographs, at age 2 days, both upper and lower limbs showed broad metaphyses and elbow contractures (Fig. 3). Cervical kyphosis with underdeveloped fourth cervical vertebrae was present at 3 months but was mostly resolved spontaneously by 5 years. Thoracic and lumbar vertebrae were of normal shape but there was significant scoliosis. Lower extremities at 5 years showed bilateral coxa vara with abnormally broad and short femoral necks and flat epiphyses, and both knees were in valgus position. Knee MRI demonstrated bilateral laterally displaced double layer patellae.

2.3. Genetic findings

Patient I had been previously diagnosed as having spondyloepiphyseal dysplasia but as the characteristics were atypical for *COL2A1*-related skeletal dysplasia, a bone dysplasia gene panel was performed at Blueprint Genetics, which indicated heterozygosity for two known *SLC26A2* pathogenic variants: c.-26+2T > C (rs386833492) and c.1957T > A (p.Cys653Ser, rs104893924) (Fig. 4). The former is a well-known disease-causing splice donor site mutation and recognized as the Finnish founder mutation for DTD (Hastbacka et al., 1999). The latter is a missense variant with pathogenic predictions by SIFT and PolyPhen and a rather low allele frequency in databases. Homozygous p.Cys653Ser has previously been described in relatively mild rMED (Mäkitie et al., 2003). The parents were healthy and were not available for genetic testing.

Genetic testing for Patient II for suspected *SLC26A2*-related disease was performed in the first days postpartum at HUSLAB (Helsinki, Finland) for the Finnish major mutations and subsequently for the whole *SLC26A2* gene. The patient was found to harbor two heterozygous missense mutations in *SLC26A2* (NM_000112.3): the common variant c.835C > T (p.Arg279Trp, rs104893915; paternally inherited) and a rare mutation c.1535C > A (p.Thr512Lys, rs121908078; maternally inherited), which has only been found in the Finnish population (submitted to LOVD, accession number 00181232) (Fig. 4). His clinical characteristics, particularly his mildly short stature, and genetic findings were not typical for DTD and his diagnosis was regarded as rMED or variant of DTD.

3. Discussion

We describe two patients with unusual combinations of *SLC26A2* mutations leading to an rMED phenotype. These patients elucidate the genetic and clinical variability of this entity and further underscore the overlap between rMED and DTD. Further, as seen in Patient II, some of these manifestations may be severe and require prompt treatment (e.g. severe cervical kyphosis, early-childhood onset scoliosis) and therefore careful follow up of these patients is indicated.

The *SLC26A2* gene comprises three exons and encodes a 739 amino acid transmembrane sulfate carrier protein (*SLC26A2*) (Hastbacka et al., 1994). Pathogenic sequence variants in *SLC26A2* cause various forms of recessive chondrodysplasias with mild to severe phenotypes including achondrogenesis type 1B (OMIM 600972), atelosteogenesis type II (OMIM 256050), diastrophic dysplasia (OMIM 222600) and recessive MED (OMIM 226900). There are 51 *SLC26A2* mutations listed in the Human Gene Mutation Database professional (www.hgmd.cf.ac.uk): 29 are missense mutations, three nonsense mutations, two splice

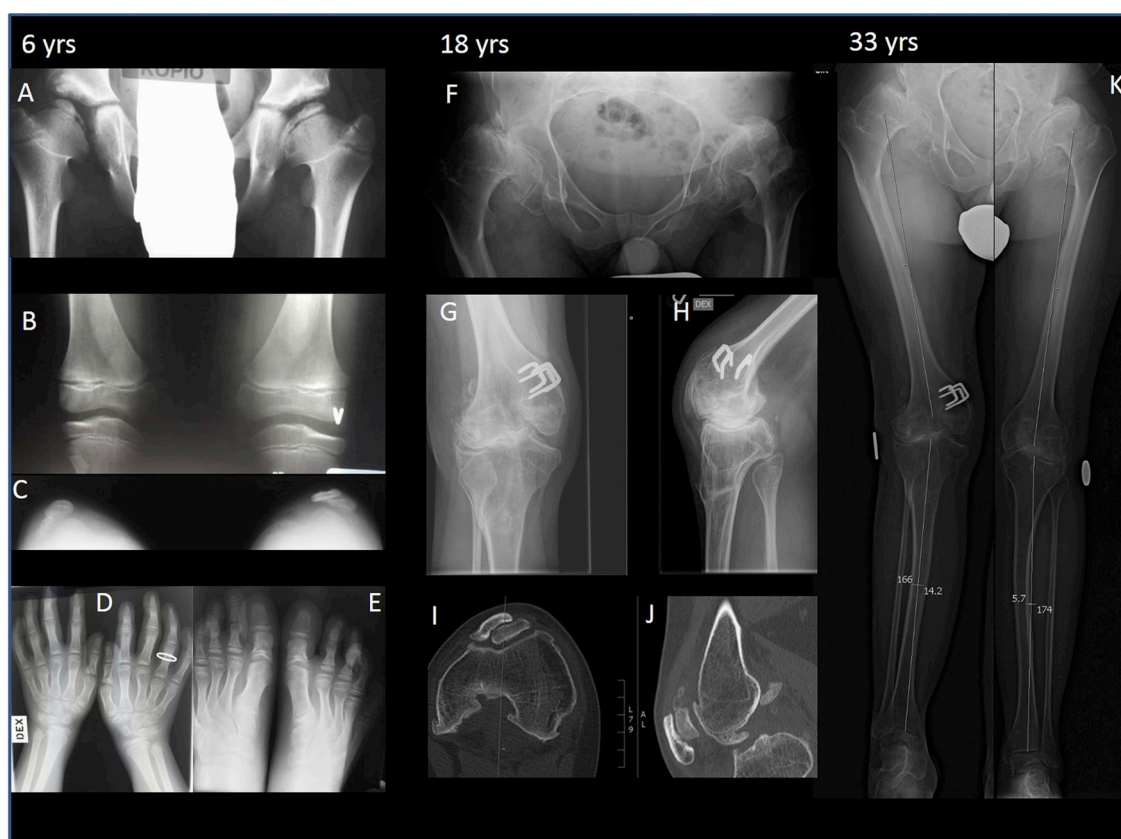


Fig. 1. Radiographs of Patient 1 from age 6 to 33 years.

- A. Hip X-rays at 6 years showed bilaterally flattened, crescent-shaped femoral epiphyses, broad and short femoral necks, and dysplastic right acetabulum.
 B. At age 6 years, epiphyses of the knees were slightly flat, and
 C. patient had laterally displaced double layer patellae.
 D. Hand X-ray of both hands showed short, “stubby” metacarpals, fourth metacarpal bones being particularly short. Epiphyses of ulna and radius were slightly flat, and there was ulnar deviation in the left wrist.
 E. All metatarsals were also short and “stubby” with flat distal epiphyses, the fourth and the fifth metatarsals being particularly short. The proximal phalanges of the both first toes had cone epiphyses.
 F. Pelvis X-ray at age 18 years demonstrated cranially dislocated right femoral head and severe hip arthrosis on both hips.
 G-H. X-rays of the right knee with severe arthrosis (metal hooks from medial epiphyseodesis operation)
 I-J. CT of the left knee with double layer patella and knee arthrosis
 K. In X-ray of the lower extremities at age 33 years there was marked arthrosis in the both hips and knees. Right hip was cranially dislocated, and right knee was in valgus position.

site mutations and 16 frameshift mutations. ClinVar (www.ncbi.nlm.nih.gov/clinvar) reports 58 *SLC26A2* variants that are classified as pathogenic or likely pathogenic. Several of these mutations have been reported as causing rMED (Table 1), the most common genotype in rMED being homozygosity for c.835C > T (p.Arg279Trp) (Bonafe et al., 2002; Barbosa et al., 2011). The phenotypic severity can be

correlated with the residual activity of the sulfate transporters resulting from different mutant alleles (Rossi and Superti-Furga, 2001; Syvanen et al., 2013).

A previous report indicated that patients with rMED may have similar cervical kyphosis as seen in DTD (Mäkitie et al., 2015). This was also seen in our Patient II. Here we further report the presence of severe

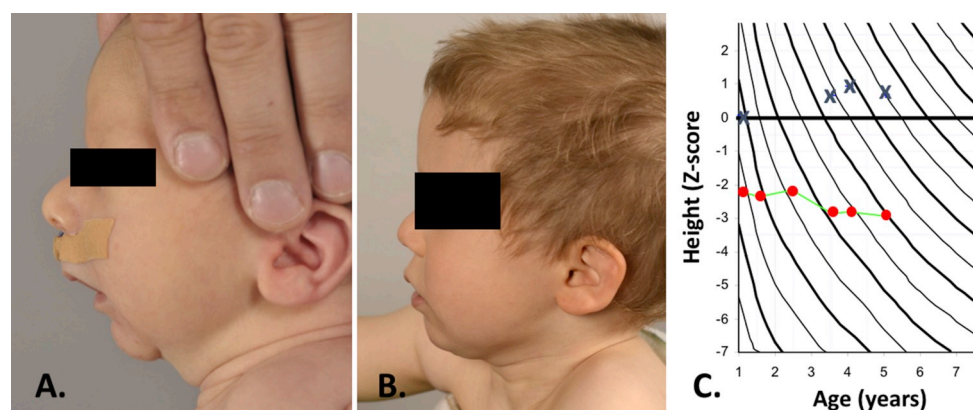


Fig. 2. Clinical features of Patient 2.

Patient 2 at 2 weeks (A.) and at 3 years (B.). The small jaw has grown spontaneously. The growth curve (dots connected by line) shows relative height deviating from -2.1 SD to -2.9 SD at the same time when scoliosis and knee valgus deformity have deteriorated. Height-adjusted weight (crosses) has remained normal.



Fig. 3. Radiographs of Patient 2 from age 2 days to 5 years.
A-B. X-rays of the right arm and C. right leg at age 2 days with broad metaphyses of the tubular bones.
D-E: In spinal X-ray at 3 months, cervical kyphosis with abnormal, underdeveloped fourth cervical vertebra was evident. Thoracic and lumbar vertebrae had normal shape, there was a slight curvature at the thoraco-lumbar level.
F-H. At 5 years of age, cervical kyphosis had resolved spontaneously, but patient had developed scoliosis (F. neck X-ray G. spine X-ray, H. spine MRI).
I: X-ray of the lower extremities at age 5 years with bilateral coxa vara with abnormally broad and short femoral necks and flat epiphyses, and both knees in valgus position.
J: In MRI (axial fat-saturated PD TSE sequence) there were laterally displaced double layer patellae in both knees.

scoliosis in a patient with rMED. Furthermore, the patient also had a very small jaw with cleft palate, reminiscent of Pierre Robin–sequence, which was also considered as his diagnosis. In 2013, Zechi-Ceide et al. reported on two siblings with compound heterozygosity for *SCL26A2* mutations p.Arg279Trp and the Finnish founder mutation (c.-26 + 2T > C) and Robin sequence, and a phenotype intermediate between DTD and rMED (Zechi-Ceide et al., 2013). Interestingly, in our patient the disproportionately small jaw has normalized by age 5 years.

Our Patient I had received a diagnosis of spondylo-epiphyseal

dysplasia, which is an autosomal dominant disease with a 50% risk of recurrence in the offspring. Careful clinical and radiographic review, combined with genetic testing, confirmed the correct diagnosis to be rMED, with remarkably lower inheritance risk even in the Finnish population with higher than normal carrier frequency for *SLC26A2* mutations.

In summary, our report further elucidates the phenotypic and genotypic variability of rMED. The severe manifestations in one of our patients highlight the need for careful clinical follow up of patients with

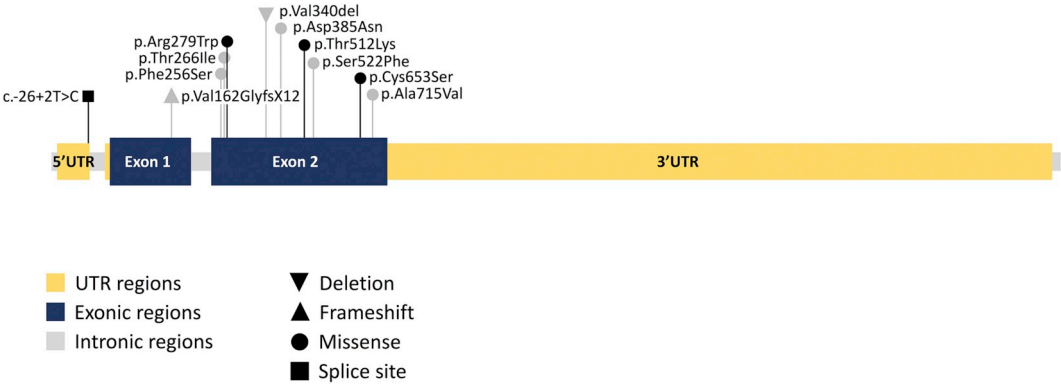


Fig. 4. Schematic presentation of rMED-causing *SLC26A2* mutations reported in literature.
The mutation types is indicated with different symbols. The *SLC26A2* mutations described in this article are marked in black and previously reported mutations in gray. UTR = untranslated region.

Table 1List of known mutations in *SLC26A2* causing rMED.

Allele A		Allele B		Phenotype	Reported by
c.862C > T	p.Arg279Trp	c.862C > T	p.Arg279Trp	rMED	Superti-Furga et al., [1999], Huber et al., [2001], Czarny-Ratajczak et al., [2010], Ballhausen et al., [2003]
c.1984T > A	p.Cys653Ser	c.1984T > A	p.Cys653Ser	rMED	Mäkitie et al., [2003], Hinrichs et al., [2010]
c.1984T > A	p.Cys653Ser	c.2172C > T	p.Ala715Val	rMED	Rossi and Superti-Furga [2001], Ballhausen et al., [2003], Jackson et al., [2012]
c.-26 + 2T > C	IVS1 + 2T	c.794T > C	p.Phe256Ser	rMED	Hästbacka et al., [1999], Jackson et al., [2012]
c.-26 + 2T > C	IVS1 + 2T	c.1984T > A	p.Cys653Ser	rMED	Hästbacka et al., [1999], Ballhausen et al., [2003], Jackson et al., [2012]
c.862C > T	p.Arg279Trp	c.1562C > A	p.Thr512Lys	rMED	Syvanen et al., [2013]
c.-26 + 2T > C	IVS1 + 2T	c.862C > T	p.Arg279Trp	rMED/DTD	Ballhausen et al., [2003]
c.485,486delTG	p.Val162GlyfsX12	c.1153G > A	p.Asp385Asn	rMED	Cho et al., [2010]
c.797C > T	p.Thr266Ile	c.1018-1020del	p.Val340del	rMED/ Desbuquios dysplasia	Miyake et al., [2008]
c.835C > T	p.Arg279Trp	c.1565C > T	p.Ser522Phe	rMED	Barreda-Bonis et al., [2018]
c.-26 + 2T > C	IVS1 + 2T	c.1957 ^a T > A	p.Cys653Ser	rMED	This report (Patient I)
c.835 ^a C > T	p.Arg279Trp	c.1535 ^a C > A	p.Thr512Lys	rMED	This report (Patient II)

^a NM_000112.3 (Reference sequence differ from older version).

rMED. Furthermore, we emphasize the importance of correct molecular diagnosis in skeletal dysplasias as this has a major impact on genetic counseling.

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Conflicts of interest

All authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejmg.2018.11.007>.

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